Patrick J. Zenner
President and Chief Executive Officer

Roche

By Hand

November 13, 2000

The Honorable Bart Stupak
United States House of Representatives
2348 Rayburn House Office Building
Washington, DC 20515-2201

Dear Representative Stupak:

We have been informed by the Food and Drug Administration (FDA) that you will be meeting with Jane Henney, Commissioner, FDA and Janet Woodcock, Director, Center for Drug Evaluation and Research, to discuss concerns relating to Accutane® (isotretinoin). In order to support that dialogue, we are hereby providing our most recent submissions to the FDA relating to Accutane risk management. As you know, in addition to the commitments made in our October 17th letter to you, we are actively working to implement additional enhancements to the Accutane risk management program in response to the recent meeting of the Agency's Dermatologic and Ophthalmic Drugs Advisory Committee, including changes relating to psychiatric issues and preventing pregnancy.

The attached submissions include:

- Our October 25, 2000, submission letter responding to FDA's requests, providing (1) a proposed Medication Guide; and (2) a revised informed consent form for all patients, both including language relating to psychiatric issues. The educational and research timelines and plans to address the psychiatric issues were also submitted in this letter.

- Our October 31, 2000, submission letter providing our initial timelines and responses to the Agency's requests for enhancements to the Accutane risk management program in regards to preventing pregnancies in Accutane patients.

Hoffmann-La Roche has engaged in years of effort, in close coordination with the FDA, to ensure safe and effective use of Accutane. We would welcome the opportunity to discuss our

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efforts with respect to Accutane risk management with you and other Members of Congress who have expressed concerns. We hope this information is helpful to you.

Sincerely,

Patrick J. Zenner

PJZ/cds

Enclosures: 2

NDA 18-662 – Accutane®
(13-cis-retinoic acid, isotretinoin, Ro 04-3780) Capsules

Meeting Request – Risk Management Program
General Correspondence – Risk Management Program

October 31, 2000

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October 31, 2000

Dr. Jonathan Wilkin
Food and Drug Administration
Division of Dermatologic & Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard, 2nd Floor
Rockville, Maryland 20850

Dear Dr. Wilkin:

Re: NDA 18-662 – Accutane (isotretinoin) Capsules
Meeting Request – Risk Management Program
General Correspondence – Risk Management Program

Reference is made to the September 18-19, 2000 meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and to the October 6, 2000 letter from the FDA summarizing the Agency's request for a detailed risk management program for Accutane. This submission contains the strategy for the development and implementation of the enhanced Accutane risk management program for pregnancy prevention. The first portion of the Accutane risk management program detailing psychiatric adverse events was submitted to the Agency on October 25, 2000.

Consistent with our past efforts with Accutane, the outlined programs emphasize collaboration with the FDA to ensure the safe and effective use of this important medication. The enhancements to our Accutane risk management program described in this submission constructively address the Agency's requests. The program proposed is unprecedented in scope for a marketed drug with such a significant patient population and prescriber base. **For these reasons, we are hereby requesting an urgent meeting with the FDA to discuss the risk management program for Accutane.** Agency participants in this critical meeting should include members of the Dermatologic and Drug Products Division and The Office of Post Marketing Drug Risk Assessment.

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act, 5 U.S.C. § 552(b)(4) and FDA regulations, and the disclosure of which is prohibited by section 301(j) of the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, 18 U.S.C. § 1905, and other applicable law. Pursuant to FDA regulations (21 C.F.R. §§ 20.45-20.46 and 20.61(e)), Hoffmann-La Roche is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please do not hesitate to contact the undersigned, if you have any questions regarding this information.

Sincerely,
HOFFMANN-LA ROCHE INC.

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Dr. Janet Woodcock, HFD-001

I. Introduction

Roche is committed to assuring that the enhanced risk management program for Accutane will be comprehensive, achievable and implemented for all patients that are prescribed Accutane. The proposed Accutane risk management program is a complex endeavor with numerous components and encompasses a variety of issues that need to be addressed and resolved in the ongoing collaborations between Roche and the FDA. This complexity necessitates iterative revisions, discussions, and agreements as the elements of the risk management programs evolve to assure that the objectives can be met as rapidly as possible. Our overriding goal is to continue to assure the safe and appropriate use of Accutane through a risk management program that patients and physicians are able to use to make truly informed decisions on appropriate health care. Concurrently, we must ensure that the privacy and rights of patients are protected, and that physicians are able to use Accutane in the practice of medicine without undue interference by third parties.

The enhancements in the risk management program for Accutane will include the following components:

1. Accutane Medication guide
2. Psychiatric education
3. Psychiatric research program
4. Informed consent for psychiatric and pregnancy issues
5. Educational program for prescribers and patients to prevent pregnancy
6. Enrollment of the patients and prescribers into a verifiable database
7. Ascertainment and follow-up of all fetal exposures
8. External monitoring program.

The October 25, 2000 submission addressed the first four components. These items will proceed with implementation as soon as agreement is reached with the FDA.

This submission outlines Roche's plans and timelines for the remaining components. Specifically, the development and implementation of an enhanced program to address prevention of pregnancy.

II. Plans and Timelines of Pregnancy Educational Elements for Prescribers and Patients (See also Appendix A).

Roche has undertaken the task to design and implement additional educational elements and programs. These components will further prepare Accutane prescribers to ensure that they are properly executing a complete pregnancy prevention program, selecting the appropriate patients, and managing the risks of therapy as specified in the label. The education component is an integral part of the program to assure progress toward the primary goals of the continued safe

and appropriate use of Accutane for all patients and, for female patients, provide a means for pregnancy prevention. The prescriber is the major conduit for the education of the patients. Patients require this information so that they can make an informed decision on the selection of their own health care. Hence, our enhanced educational elements provide components for the education of the patient as well as of the nursing and pharmacist communities.

A. Education Elements Developed: Implementation Plan[1]

Outlined below are the proposed implementation plans for the elements of the program described in Appendix A.

1. Prescriber Education

Accutane prescribers[2] will be notified of the educational revisions to the Pregnancy Prevention Program (PPP) by November 2000. Each new Accutane prescriber will be mailed information on the PPP monthly.

Roche will also sponsor an Accutane Continuing Medical Education (CME) certification course for prescribers, in order to update prescribers on the potential for serious adverse events with special reference to contraceptive counseling. This CME course is in preparation and is currently planned for completion in February 2001. This program will be a component to prescribing Accutane and entering patients into the Accutane Prescriber and Patient Database (described below).

Publication of The Accutane Health Professionals Guide is planned for November 2000.

Publication of *Best Practices for Prescribers* is planned for the first quarter of 2001 and will incorporate prescriber registration information.

2. Nursing Education

Publication of the *Dermatology Nursing* articles on the Pregnancy Prevention Program as a supplement is planned for the first quarter of 2001 and will contain information about registration for patients.

Publication of the *Nurse Practitioner* articles on the Pregnancy Prevention Program supplement is planned for the first quarter of 2001 and will contain information about registration for patients and prescribers.

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[1] Note: Additional educational elements will be added regarding the objectives and utilization of the Accutane Prescriber and Patient databases as the details of the program evolve. These additional elements will be distributed to prescribers, pharmacists, and patients.

[2] As identified by the IMS database identified during the previous two years up to and including October 2000.

A Contraception Counseling Certificate Program for registered nurses, and medical assistants is ongoing. A program for eight Dermatology Nurses' Association Regional Chapters will be completed by December 2000 and 27 Dermatology Nurses' Association Regional Chapters will have completed this program by December 2001.

3. Pharmacist Education

Publication of an article for pharmacists on the Pregnancy Prevention Program is planned for the first quarter of 2001 and will contain information about the confirmation of negative results from pregnancy testing.

A pharmacist newsletter relating to the PPP will be published in November 2000.

A pharmacist Continuing Education Unit (CEU) Article on Accutane adverse events is scheduled for March 2001.

4. Patient Education

Publication of *Be Smart, Be Safe, Be Sure* patient materials, including the enhanced 10 Step process, is planned for implementation in the first quarter of November 2001.

III. Plans and Timelines for Development and Implementation of :

- REGISTRATION FOR ALL ACCUTANE PATIENTS
- REGISTRATION FOR ACCUTANE PRESCRIBERS,
- ASCERTAINMENT AND FOLLOW-UP OF ALL PREGNANCIES
- EXTERNAL MONITORING PROGRAM

A. Accutane Prescriber and Patient Database:

1. Prescribers would register with Roche based on a CME program for Accutane-specific risk management with specific reference to pregnancy prevention including contraceptive counseling.

2. This prescriber registration is required in order to access software, which generates an exclusive Accutane prescription. The special prescription would only be generated once all the preconditions are met. That is, when the patient demographic fields are entered, an informed consent is obtained, and, for female patients, two initial and subsequent monthly pregnancy tests are checked. Informed consent

for female patients would include consents to be registered and followed up[3].

3. Pharmacies would only dispense Accutane based on this special Accutane prescription, within a specified period.

4. Data from the physician's office would be transferred to a central database.

5. The Accutane Pregnancy Survey (managed by Slone Epidemiology Unit) using the central database, would follow up on all registered female patients for presence or absence of pregnancy, and ascertain pregnancy outcomes.

The proposed process for developing a prescriber and patient database provides for:

- A registry and qualifications required for practitioners
- An inventory of all patients, both male and female
- A comprehensive program to track and report to CDER
  - all reported fetal exposures to Accutane
  - the outcomes of such exposures
- Dispensing of Accutane to female patients only upon verification of adequate pregnancy testing.

B. External Monitoring/Oversight

Roche would explore establishing agreements with pregnancy risk organizations such as the Center for Disease Control (CDC), and with organizations containing expertise in women's health and reproductive issues. These groups would be encouraged to use a standardized data collection form to report pregnancies that occurred while on Accutane, with the objective of matching these reports to those in the Accutane Prescriber and Patient Database.

Roche will also explore the possibility of obtaining data on pregnancy exposures to Accutane from managed care and other external databases, in order to match externally reported exposures to the Accutane Prescriber and Patient Database. We propose a quarterly review of the data for the first year and then annual

[3] A proposed interim informed consent for all adverse event warnings including psychiatric events was submitted to the FDA October 25, 2000 for use with all patients. In addition, for females an Accutane informed consent, as approved by the FDA in May 2000, is currently available to female patients through the PPP. As explained an informed consent for all patients will be developed as an element of the enhanced Accutane Pregnancy Prevention Program to assure that informed consent is obtained concerning the database collection and re-contact procedures for female patients.

review of the program and the external data by a joint FDA/Roche monitoring group.

This proposed program has the potential to meet all of the requirements requested but will need discussion and resolution of the underlying critical issues, including the components of its design and implementation programs to assure that it is sustainable and is supported by major stakeholders: patients, prescribers, pharmacists, regulators, federal and state legislators, and institutional review boards.

C. Considerations Regarding Design, Development, and Implementation

The primary goals of this pregnancy risk management program are to ensure that no patient begins therapy if pregnant, and that no pregnancies occur while on Accutane therapy. Other pregnancy registries and programs exist but have substantial differences in intentions and/or context than the program proposed for Accutane. The Accutane patient and healthcare professional populations present unique challenges to the design and implementation of this proposed risk management program.

Accutane is a marketed drug with a long history of use (18 years) with a resultant high level of awareness of its unique benefits among a large number of practitioners and patients. Prescribers believe they are knowledgeable of the safety profile of Accutane and of appropriate management of patients. In addition, most of the 200,000 female patients are young, and otherwise healthy. Protecting patient privacy and patient rights for this population creates unique challenges to a successful and sustainable program for Accutane. Therefore, policy and legal issues that can arise due to changes in patients' and prescribers' rights from this risk management program may become important where they have not been in the past.

These issues need to be addressed to design and implement a registration program that assures complete capture of the total denominator of Accutane users, both male and female, and to establish the numerator of the total number of fetal exposures in the Accutane exposed female population

We intend to move forward on a collaborative basis with the OPDRA and the division at the Agency to address the critical issues that will need to be resolved before this program can be effectively developed and reliably implemented:

1. Risk management and Registration Programs

In order to make the proposed Accutane risk management program feasible, acceptable and sustainable, it is necessary to elicit the knowledge on the technical aspects and issues encountered in other risk management programs.

Most of these aspects are not available in publications but may be known in the agency.

Previous registries and risk management programs have been characteristically established as elements of the approved labeling and conditions for marketing, or very soon after marketing before the benefits and patterns of use of the medication have become established. Thus, issues concerning patients' rights and access to treatment and prescribers' rights and prescribers' obligations may have not yet arisen in these programs. In contrast, Accutane has been on the market for 18 years, and therefore, execution of the prescriber and patient database could be perceived to impose untoward burdens on both prescribers' and patients' rights and practices among those who are already prescribing or taking Accutane. There is no registry or database in the healthcare arena which ensure 100% compliance with registration of over 500,000 patients and more than 10,000 prescribers.

2. Alternative pregnancy prevention programs

There is only one other pregnancy prevention program available for a medication: STEPS program for thalidomide. The intricate structure and the outcomes of this program are not available to Roche either as publications or presentation. However, it is known that the female population differs substantially from the Accutane population. The thalidomide female patients are older, sicker, less sexually active and are at least three orders of magnitude fewer in number. If the STEPS program elements were to be applied to this program, then significant changes may be required to meet the necessary criteria and functionality for the Accutane database.

In addition, thalidomide is currently only available in the United States, which limits its alternative distribution channels (e.g. offshore Internet dispensing). Isotretinoin, however, is available worldwide in many countries, and accessibility through these channels has been documented. These channels have the potential to significantly enable patients to access isotretinoin outside of the protection of the Accutane risk management program, and thereby negatively affect its success.

3. Unique medication

Accutane is a uniquely effective therapy for severe recalcitrant nodular acne, which, if not treated, often results in permanent disfigurement. In many cases, a single course of Accutane therapy is curative.[4] There is no alternative therapy as effective as Accutane for this condition that patients may use if they are denied or refuse Accutane therapy. Therefore, legitimate concerns may exist about the requirement that patients participate in the registry and pregnancy follow-up, as a

[4] **FDA Briefing Document; Correspondence August 28, 2000.**

condition of receiving appropriate medical treatment (Accutane), which they would otherwise be qualified to receive, based on their own and their physicians' determination of risk and benefit, and for which there is no alternative.[5] The potential issue of a patients' rights to receive appropriate medical treatment, if they refuse to grant permission to be registered or to be "tracked" by the pregnancy registry needs to be clearly addressed.

4. Issues of Informed Consent and Confidentiality

The large number of Accutane patients and prescribers distinguishes this program from other registries. Other registries did not have to resolve the complications of obtaining informed consent, maintaining confidentiality and ascertaining accurate information in such large numbers of patients and prescribers.

Registration of patients below age 18 in the proposed Accutane prescriber and patient database will necessitate obtaining informed consent from parents, while maintaining confidentiality of the minor's, as well as others, sexual history and contraception use. The confidentiality of post Accutane therapy contacts for additional information regarding pregnancy status, pregnancy follow-up and the patients' methods of preventing pregnancy also needs to be protectedIn some contexts the collection of patient demographics and the follow up of patients for ascertaining private medical information may be viewed as research since collection of such data are designed to develop or contribute to generalizable knowledge.[6] Thus, should elements of the Accutane database be construed as research in any context, this could affect the structure of the program. Moreover, privacy rights have become and will continue to be a vital focus in the public, Congressional and regulatory arenas. As collection of extremely sensitive data will be critical to the success of the Accutane PPP, the potential for compelling patients to forgo their privacy and/or confidentiality rights in order to receive treatment needs to be addressed. It should be noted that in many practices, the content of an informed consent for Accutane patients would need to be reviewed by Institutional Review Boards (IRB). All informed consents for the Accutane pregnancy registry will also be reviewed by the IRB responsible for the Slone Epidemiology Unit (SEU).

In view of these issues, it is critical that the Agency involves the Office of Human Research Protection (OHRP/DHHS), in our discussions with OPDRA and the division to assist us in resolving this potential regulatory conflict.

5. Pharmacy issues

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[5] See, e.g., FDAMA § 211 (amending section 519 of the FD&C Act to allow patients to refuse to release identifying information for device tracking purposes).

[6] See e.g., 45 CFR 46.101 et seq. (Basic HHS Policy for Protection of Human Research Subjects)

In the proposed program, the role of the pharmacist is limited by dispensing Accutane only based on the special prescription. Nonetheless, issues relating to confidentiality of patients' medical information, possible interference with the practice of medicine and the possibility of increased liability risks for pharmacists could be raised.

The ethical duty of a confidential physician-patient relationship, such as verification of a positive pregnancy test, (e.g. via information on a prescription or in a database) may not necessarily extend to the pharmacist-patient relationship in every instance The American Pharmaceutical Association's Code of Ethics is not imposed upon pharmacists by statute or common law in all states--particularly with respect to pharmacy records

The scope of pharmacy involvement for this database will be significantly larger than any other current database. Most registries either do not require pharmacy compliance at all or are limited to a select number of pharmacies. The ability to enabling pharmacists to comply with limiting dispensing of Accutane to patients with special prescriptions while maintaining the confidentiality of patients is a critical concern for successful implementation.

In summary, the following critical issues have the potential to affect the design and implementation of an Accutane risk management system:

1. Burden on prescribers' and patients' rights
2. Alternative distribution channels
3. Alternatives for patients' medical therapy
4. Obtaining appropriate informed consent
5. Extended role of pharmacists

Careful construction of this risk management program will be necessary so that it enhances the existing pregnancy prevention program, which had achieved an observed pregnancy rate of 10% of that observed with normal contraceptive practice. Additionally, consultation with and acceptance by different stakeholders will be necessary, since any component could be strongly challenged and such challenge could require radical redesign of program elements. While minor revisions are anticipated after the launch of this program, significant redesign would add substantial delays in accomplishing the goals for pregnancy prevention.

Therefore, to resolve these issues before implementation, we will need input and guidance from OPDRA and the division as well as from the Office of Human Research Protection (OHRP/DHHS). We propose that during this critical period of resolving these issues and obtaining input and guidance on the design elements that we establish close iterative collaborations to be able to finalize these issues.

D. Timelines

In order to assure sustainability and success of this program several elements should take place:

1. A review of the details and performance of existing programs and registries with information from the FDA will provide guidelines for determining the most appropriate elements for application to the Accutane program.

2. A resolution of the critical issues regarding patients rights, prescriber certification, the role of informed consent and maintaining patient confidentiality need to be reached to assure objectives are met.

Therefore, a joint Roche/FDA dialogue to initiate a critically urgent discourse on the design elements and to resolve specific issues is requested as soon as possible. We propose that this will initiate a dialogue every two weeks with a resolution of these design and issues within three months.
Roche is prepared to proceed immediately with the development of a comprehensive registration program as soon as joint discussions with the FDA have resulted in an agreement on the design (anticipated to be by the end of January 2001). A database would be finalized, internally validated, and tested in approximately three months. A limited pilot program to appraise the elements in a real world situation, which will take approximately 2 months to accomplish and evaluate, will follow this. Following the successful evaluation of the pilot, anticipated to be July 2001, the dissemination of the program to registered Accutane prescribers would begin and the limitation of dispensing of Accutane, to the special prescriptions only by pharmacies, would start within two months.

Moreover, there are elements of the risk management program that can be executed on a rolling basis as components are agreed upon and implementation plans are put in place. Three elements can be established in this category:

- Interim Informed consent
- Medication Guide
- PPP patient and prescriber educational pregnancy prevention brochures

Appendix A. Educational Program

The FDA has requested that Roche initiate an enhanced educational program for each Accutane patient and/or parent/guardian (if the patient Is under 18 years of age). This educational program is to include verifiable documented written informed consent by all patients and/or parent/guardian (if the patient is under 18 years of age), both male and female, before receiving Accutane.

Informed Consent:
The matter of the proposed changes to the Accutane informed consent was addressed in the submission to the FDA of October 25, 2000.

Prescriber Education

There are several components to the prescriber educational program. These components assure that prescribers are aware of current Accutane labeling.

Roche will also sponsor an Accutane Continuing Medical Education (CME) certification course for prescribers, in order to update prescribers on the potential for serious adverse events. This course will have the following curriculum:

- Pre testing on adverse events in the product information with an emphasis on teratogenic potential
- Review of current label and data supporting inclusion in label
- Potentially teratogenic drugs already used in dermatology
- Contraception methods and failure
- Assessment of patients' potential pregnancy risk
- Current pregnancy testing methods
- Post testing

The Accutane Health Care Professionals Guide has been created. The publication reviews and reemphasizes the need for the current Pregnancy Prevention Program[SM]

A new publication for prescribers entitled *Best Practices for Prescribers* has been created and will be submitted to the FDA. The publication contains:

- A summary of a review of 10 years of data on pregnancy exposure;
- The importance of the Accutane Patient Survey;
- An assessment of patient compliance;
- Information about contraception methods and failure rates;
- Information on emergency contraception methods;
- Education on recognizing and responding to early symptoms of pregnancy;
- Detailed education on administering and interpreting pregnancy testing; and
- Methods for assessment of pregnancy risk using a sexual history algorithm.

A supplement to professional medical journals on Accutane, teratogenic risk, and required pregnancy testing and contraception methods is planned for the first quarter of 2001. The supplement titles include:

- Guidelines for Practice: Caring for Women of Childbearing-Potential Taking Teratogenic Drugs in Dermatology
- Sexual History and Counseling for Patients on Teratogenic Drugs
- Contraception: Myths/Facts and Methods
- *Be Safe, Be Smart, Be Sure*: The Revised Pregnancy Prevention Program for Women on Accutane (isotretinoin)

Nursing Education

A program for Continuing Education Units (CEU), which has the approval of the Dermatology Nurses' Association (DNA) is being presented at DNA State chapter meetings as well as the DNA national conference in 2001. Registered nurses, licensed practical nurses, and medical assistants will receive a certificate of completion in Contraception Counseling.

Pharmacist Education

Information will be distributed to pharmacists, detailing the 30-day dispensing limit for Accutane and the need to enforce the "No Refills" requirement of the product label for Accutane patients. The following booklets will be made available to pharmacists for distribution to their female Accutane patients of reproductive potential:

- *Important Information Concerning Your Treatment with Accutane® (isotretinoin)* –7th Edition
- *Preventing Pregnancy: A Guide to Contraception*SM
- *Treatment with Accutane® (isotretinoin) -- What Male/Female Patients Need to Know*

An article, with a supported CEU option, will be published in a peer-reviewed journal on The *Roche PPP Program - The Pharmacist's Role as PPP Counselor.*

Patient Education

Education for male and female patients has been published in the new, May 2000 *Important Information Concerning Your Treatment with Accutane® (isotretinoin)* –7th Edition.

A revision of the current PPP patient folder, Be Smart, Be Safe, Be Sure, will contain a 10 Step program that will be followed in order to qualify a female patient before a prescription for Accutane is written. The 10 steps are a

progressive learning system that allows a patient to build on previous information and instruction by the prescriber. The ten steps include:

Table 1 Enhanced 10-Step Program

Step	Element	Information
1	Qualification Checklist	Criteria for selecting female patients
2	*Important Information About Your Treatment with Accutane (isotretinoin)* – 7th Edition	Warnings and Adverse Reactions
3	Self Evaluation Quiz	Knowledge about Accutane
4	Contraception Counseling Referral Program	Establishing that patients have access to contraception
5	Information/Consent Form	Affirming that patients understand and agree to commitment
6	Accutane Survey Enrollment Form	Insuring a method to increase pregnancy database
7	Be Prepared, Be Protected video	Alternative to written pregnancy risks
8	Prevent Pregnancy: A Guide to Contraception	Insuring that females obtain contraception knowledge
9	Contraception Knowledge Test	Insuring that female patient understands contraception information
10	Accutane InfoLine/ Confidential Contraception Counseling Line	Providing alternative languages and providing 24 hour, 7 day access to contraception information

Each Step in the program increases the patient's information and builds knowledge for the next step; the enhanced 10-Step program also provides information in a variety of media. By following the program systematically, the 10 step program assures that all the necessary building blocks of the PPP will be implemented for each and every female patient, who is to receive Accutane.

Step 1. The Qualification Checklist included in the original PPP provides a tool for assessing the proper selection of patients.

Step 2. The booklet *Important Information Concerning Your Treatment with Accutane® (isotretinoin)* – 7th Edition provides information about Accutane efficacy while including information about contraindications, warnings, and side effects. The booklet is updated to reflect changes in the Accutane product information.

Step 3. The Self-Evaluation Quiz provides an opportunity for female patients to realize the commitment that must be made before they can take Accutane.

Step 4. The Contraception Counseling Referral Program is updated to include all those health care professionals that are licensed to provide contraceptive advice; all referrals continue to be reimbursed by Roche directly.

Step 5. The Information/Consent Form, updated to meet label requirements, provides for the selection of one primary and one secondary birth control method by the patient. This form serves to confirm awareness of the risks of using the drug during pregnancy and to confirm that female patients are capable of avoiding pregnancy throughout therapy.

Step 6. The Accutane Survey Form provides a method for the prescriber to obtain the female patient's permission to transfer her coded information to the Slone Epidemiology Unit (SEU) database.

Step 7. The video *Be Prepared, Be Protected* is non-branded and provides five scenarios about women who are having difficulty with contraception; each scenario is followed by comments by a counselor who provides the solution to that scenario. The patients may keep the video to review at home with family and possibly with a partner who is having difficulty with the need for two methods of contraception.

Step 8. The new *Preventing Pregnancy, a Guide to Contraception* booklet uses the change in technology and open communication to answer questions about contraception methods and failure rates, as well as myths and facts about pregnancy.

Step 9. After reading the Preventing Pregnancy booklet, the female patient is asked to complete a Contraception Knowledge Test, designed to assess both her compliance attributes and her knowledge and skill relative to contraception.

Step 10. The Accutane InfoLine continues the tradition of the Alert Line providing Accutane information in the 13 most common languages spoken in the United States. The Confidential Contraception Counseling Line is being added to provide a means for patients to obtain confidential information about contraception 24 hours a day, 7 days a week. The patient calls a toll free number to obtain information on a variety of subjects, selected from a menu by category:

- Birth defects / teratogenicity
- Sexual intercourse and birth control
- Contraceptive methods
- Emergency contraception
- Pregnancy and pregnancy testing

NDA 18-662 – Accutane®
(13-cis-retinoic acid, isotretinoin, Ro 04-3780) Capsules

General Correspondence – Risk Management Program

October 25, 2000

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October 25, 2000

Dr. Jonathan Wilkin
Food and Drug Administration
Division of Dermatologic & Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Boulevard, 2nd Floor
Rockville, Maryland 20850

Dear Dr. Wilkin:

Re: NDA 18-662 – Accutane (isotretinoin) Capsules
General Correspondence – Risk Management Program

Reference is made to the September 18-19, 2000 meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and to the October 6, 2000 fax from the FDA summarizing the expected sponsor initiated actions regarding a risk management program for Accutane. The program Roche is developing will be submitted to the Agency in two parts. This submission not only details Roche's plans for management of psychiatric adverse events, but it also contains the first proposed drafts of the Medication Guide and Informed Consent. **The risk management program for pregnancy prevention will constitute the second submission and, as per the referenced FDA fax, will be submitted by October 31, 2000.**

The following pages describe Roche's commitment to complying with the agency's requests pertaining to risk management. Consistent with our past efforts with Accutane, the outlined programs emphasize collaboration between the sponsor and the FDA to ensure the safe and effective use of this important medication. This submission also contains four attachments:

- Attachment 1: Draft Informed Consent
- Attachment 2: Draft Medication Guide
- Attachment 3: Research Program
- Attachment 4: List of possible experts to assist in program development of the Research Program

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to exemption 4 of the Freedom of Information Act, 5 U.S.C. § 552(b)(4) and FDA regulations, and the disclosure of which is prohibited by section 301(j) of the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, 18 U.S.C. § 1905, and other applicable law. Pursuant to FDA regulations (21 C.F.R. §§ 20.45-20.46 and 20.61(e)), Hoffmann-La Roche is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

Please do not hesitate to contact the undersigned, if you have any questions regarding this information.

Sincerely,
HOFFMANN-LA ROCHE INC.

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RBK/gb

Attachments

HLR No. 2000-2650

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Dr. Diane Murphy, HFD-002
Dr. Jonca Bull, HFD-105
Dr. Peter Honig, HFD-400

INFORMED CONSENT (Attachment 1)

There will be one informed consent for both male and female patients. The core of the proposed **Informed Consent for All Accutane Patients** details the following topics:

1. Medication to treat severe recalcitrant nodular acne
2. Psychiatric conditions
3. Serious and unwanted adverse events
4. Sharing of medication
5. Donation of blood
6. Medication Guide availability
7. Patient confirmation of understanding all information received
8. Withdrawal of treatment

This informed consent thus contains information specified in the current Accutane label, including those relating to psychiatric events. We would appreciate FDA's review and comments on the proposed language within 10 working days in order to expedite this component the risk management program.

Steps to implement the use of the **Informed Consent for All Accutane Patients** will begin immediately after approval of the form from the FDA. Within six weeks after approval, the **Informed Consent for All Accutane Patients** will be produced and disseminated to prescribers and pharmacists. During this period, and until the full risk management program and the Pregnancy Prevention Program (PPP) is instituted, all female patients will need to sign <u>two</u> informed consents:

1. The interim **Informed Consent for All Accutane Patients** (proposed herein), and
2. The informed consent already in the package insert labeling and supplied as a component of the current PPP.

A single informed consent with sections for both males and females will be a component of the risk management program for Accutane. The final complete informed consent will be modified to clarify and assure that Accutane patients are fully aware that they will be registered in a confidential Accutane Patient and Prescriber database. Furthermore, all female patients must fully understand that after being registered in the confidential database, they will be contacted by the Accutane Pregnancy Registry to collect additional information on their contraceptive methods and to ascertain the effectiveness of preventing pregnancy. Thus, the format and language for this final informed consent will be composed by combining the following information into one document:

- The wording in the interim **Informed Consent for All Accutane Patients** (draft copy in Attachment 1 to this submission)
- Current Accutane Informed Consent (from current Package insert) with information on preventing pregnancy
- Information to assure consent and assure awareness from each patient that information is being collected for addition to the Accutane Patient and Prescriber Database
- Information to assure consent and assure awareness from all female patients that they will be contacted by the Accutane Pregnancy Registry

This overall implementation plan allows for a rapid interim dissemination of both an informed consent and Medication Guide for all patients. As the full risk management program for

Accutane is implemented, a full informed consent with the components of this program and the Pregnancy Prevention Program will be disseminated.

ACCUTANE MEDICATION GUIDE (Attachment 2)

The proposed wording and format of the Accutane Medication Guide is based on the regulations for Medication Guides (21 CFR 208). It is composed of two sections. The majority is for all patients but there is one section "ESPECIALLY FOR FEMALE PATIENTS" that contains the information from the boxed warning to inform patients to prevent pregnancy. This format is to assure that male patients are fully informed about their Accutane treatment, but not so overwhelmed with information not necessarily pertaining to them that they do not read the Medication Guide at all. There will be reminders throughout the final produced copy directing patients to read the sections describing the risks and use and for female patients to read the appropriate section. We would appreciate FDA's review and comments on the proposed language within 20 working days in order to expedite this component the risk management program.

As requested, the Medication Guide will be produced in two, distinct formats to ensure that every patient receives the important information. Both versions will be submitted to the agency in full color for approval. Within six weeks of full language approval of the Medication Guide, the sponsor will distribute one version to all prescribers and pharmacists so that it can be given to each Accutane patient at every opportunity and at every prescription event. Simultaneously, the sponsor will begin incorporating the Medication Guide into each new Accutane blister pack produced. This second version becomes an integral part of each new package. As per the regulations for the Medication Guide, the current professional product labeling for Accutane will be updated and submitted in the near future to reflect this important change.

PRESCRIBER EDUCATION PROGRAM

Roche will use experts, such as Drs. Douglas Jacobs and John Koo, the American Foundation of Suicide Prevention and/or the National Mental Health Association, to develop programs/educational pieces to educate prescribers about psychiatric conditions and the needs and methods to evaluate patients. The educational component could include the currently programs developed to inform general practitioners (non-psychiatrists) on methods to evaluate patients concerning symptoms of psychiatric conditions and appropriate referral procedures. Disseminated information in an educational brochure would include a literature review, simple assessment tools and referral guidelines for psychiatric conditions.

The components of this program have not been discussed in detail as yet due to the time constraint, but our plans are to implement as rapidly as possible and provide to the FDA monthly updates on the progress. The entire program will be available by April 2001.

RESEARCH PROGRAM (Attachments 3 & 4)

Roche will continue to execute a research program for psychiatric conditions. Roche has undertaken six separate studies or investigations to address psychiatric conditions to evaluate the potential association with Accutane therapy. These investigations with their principle objectives and findings are presented in Attachment 3. The FDA has received information on each of these programs except the epidemiology investigation conducted on acne patients in the United Health Care program. This report and others completed reports will be sent to the FDA by the end of November.

The complexities of continuing a program to clarify further the nature, etiology, and strength of Accutane association are extensive and include, but are not limited to the following issues:

- As Accutane is uniquely effective in severe recalcitrant nodular acne there are ethical issues with using either a placebo or other medications (which are less effective for this indication) for a disease which has permanent scarring as a likely sequelae.
- Because 99% of all patients receiving Accutane experience mucocutaneous side effects, blinding will be difficult to achieve and is critical if psychiatric endpoints are to be studied.
- For cohort studies, it will be difficult to find matching cohorts with the same type of acne disease severity and history that had not been healed with Accutane and to prospectively recruit them for the above reasons.
- It will be difficult to ascertain the relative risk of psychiatric events attributable to Accutane if a comparison group is not used.
- Selection of appropriate surrogate markers will be critical for mechanistic studies.

Consequently, to address these issues, Roche and the FDA should receive guidance from a panel of experts that consists of a consortium of clinical scientists from dermatology, epidemiology, and psychiatry. A partial list of potential experts for this Protocol Design Committee is included in Attachment 4. In order to address the initial issues, we recommend to meet with appropriate representatives of the National Institutes of Mental Health (NIH), Division of Dermatologic and Dental Drug Products, the Division of Neuropharmacological Drug Products and the Office of Post Marketing Drug Risk Assessment by the end of November to establish an agenda and the objectives for this expert panel.

This meeting has the potential to decide an appropriate program to resolve many issues that challenge the objectives of investigating the nature, etiology, and strength of association between psychiatric events and Accutane. Therefore, the following elements will need to be discussed by the panel, the Sponsor and the FDA at the Protocol Design Meetings:

1) *Objective of studies* – Study scope and hypothesis to be tested in the trial. Potential study objectives could include:

    - Determine whether there exists any causative mechanisms of Accutane associated psychiatric events
      - Purpose is to reduce uncertainty of psychiatric signal by evaluation of physiological psychiatric mechanisms in a cohort of treated subjects.
    - Determine whether there exists a change in incidence rate of psychiatric adverse events for Accutane-exposed patients.
      - Purpose is to determine what effect Accutane may have on the background incidence rate of psychiatric conditions.

2) *Study Population* – Eligible study groups and consideration of baseline stratification according to:

- Age
- Gender
- Acne Disease State
- Baseline/Historical Psychiatric Condition
- Availability of databases with size, coding, and appropriate population definitions

3) *End Points* – Potential criteria and diagnostic or screening tools for the primary & secondary endpoints

- Suicidal Behavior
- Depressive Symptoms
  - Atypical Depression
  - Brief Recurrence Depression
  - Major Depressive Disorder
- Physiological markers of depression or other psychiatric conditions
- Identification of confounders

4) *Study Design* – What factors need to be addressed in order to minimize potential bias

- Enrollment Criteria
- Comparison Group Selection
- Duration of Assessments
- Frequency of Assessments
- Assessment Tool
- Consistency of assessment criteria
- Power-analysis assumption to determine numbers to be evaluated

The potential opportunity to thoroughly study a cohort of Accutane exposed patients over an extensive period of time is one that requires careful consideration. The guidance that would come from the panel's contribution would allow Roche and the FDA the best chance of designing studies that would resolve the present uncertainty.

Due to the logistic complexities of assembling this panel of experts, Roche would convene this Protocol Design Committee within 90 days of October 31, 2000 (i.e. by January 29, 2001). When the committee provides guidelines, a trial protocol would be submitted to the FDA within 50 days and institution of the program can commence within 60 days post FDA approval.

{Interim Patient informed consent for use pending FDA approval of final informed consent}

PATIENT INFORMED CONSENT FORM:

To be completed by the patient, parent/guardian*
and signed by prescriber.

Please read each item below and initial in the space provided to indicate that you understand each item and agree to follow your prescriber's instructions. DO NOT SIGN THIS INFORMED CONSENT FORM AND DO NOT TAKE ACCUTANE IF THERE IS ANYTHING THAT YOU DO NOT UNDERSTAND. **A parent or guardian of a minor patient must also read and understand each item before signing the consent.**

1. I, _____,
(Patient's Name)
understand that Accutane is a very powerful medicine that is used to treat severe nodular acne that did not get better with other treatments including oral antibiotics.

   Initials: _____

2. I understand that there are serious and unwanted effects that I may experience while taking this medication and these have been explained to me. The most serious effect is that it causes serious birth defects.

   Initials: _____

3. I understand that there are some Accutane patients who have become depressed, had mood changes, and, in rare instances had suicidal thoughts, made suicide attempts or committed suicide. Some patients have had additional signs of anxiety and depression while taking Accutane. While it is not known if Accutane caused patients to behave this way, it is important that if I have changes in mood, sleep patterns, or irritability or have thoughts of suicide that I will immediately inform my prescriber of these changes. I will tell my prescriber if I have a history of depression, psychosis, or suicidal behavior or if I am taking medication for any of these problems.

   Initials: _____

4. Accutane has been prescribed specifically for me – I will not share Accutane with other people.

Initials: _____

5. I will not give blood while taking Accutane or for one month after stopping Accutane treatment. I understand that if someone else, who is pregnant, receives my donated blood; her baby may be exposed to Accutane and may suffer serious birth defects.

Initials: _____

6. I am aware a Medication Guide containing important information will be provided to me when I receive my medication and I will read this information prior to taking Accutane.

Initials: _____

7. My prescriber has answered all of my questions about Accutane and has provided me with information about Accutane (verbally and through the patient's information brochure). I understand all the information I have received.

Initials: _____

8. My use of Accutane is a decision between my prescriber and me. I understand that I may stop taking Accutane at any time, even after signing this form. I agree to let my prescriber know if I stop taking this medication

Initials: _____

I now authorize my prescriber _____ to begin my treatment with Accutane.

Patient signature: _____
Date: _____

Parent/guardian signature (if minor*): _____
Date: _____

Please print: Patient name and address_____

_____ Telephone (___.___.___)

I have fully explained to the patient, _____, the nature and purpose of the treatment described. I have asked the patient if he/she has

any questions regarding his/her treatment with Accutane and have answered those questions to the best of my ability.

Prescriber signature: _____ Date: _____

*If patient is a minor under the age of 18.

MEDICATION GUIDE

ACCUTANE® (Ack T) Capsules
(isotretinoin)

Please carefully read all of this information every time you receive a prescription for Accutane. New information may have been added since the last time that you received a prescription. This information does not take the place of talking with your prescriber.

What is the most important information I should know about Accutane?

Accutane is a medication used to treat patients with a severe form of acne known as severe recalcitrant nodular acne that does not respond to other treatments. There are **serious and unwanted effects** that may occur while taking this medication.

The most serious effect of Accutane is that it causes birth defects if taken by a female patient when pregnant. You must not take Accutane if you are pregnant, plan to become pregnant, or unexpectedly become pregnant during Accutane treatment. All women should read the section ESPECIALLY FOR FEMALE PATIENTS (SEE BELOW) in this Medication Guide for additional important information and warnings about Accutane and pregnancy.

You should understand that there are some Accutane patients who have become depressed, had mood changes, and, in rare instances had suicidal thoughts, made suicide attempts or committed suicide. Some patients have had additional signs of anxiety and depression while taking Accutane While it is not known if Accutane caused patients to behave this way, it is important that if you have a change in mood, sleep patterns, or irritability or have thoughts of suicide that you will immediately inform your prescriber of these changes

Be sure to tell your prescriber if you or someone in your family has a history of depression, psychosis, or suicidal behavior or if you are taking medications for any of these problems.
Additional information on these conditions are found at www.nmha.org/

A condition called pseudotumor cerebri, which is high pressure in the brain, has also been reported in some patients that have taken Accutane. You should always tell your prescriber if you have headaches with nausea and vomiting or visual disturbances.

Some patients report having acute pancreatitis. You should tell your prescriber if you have severe stomach and bowel pain, diarrhea, rectal bleeding, yellowing of your skin or eyes, or dark urine while taking Accutane.

In addition tell your prescriber about changes in your hearing, allergic reactions, bone and muscle pain, blurred vision, changes in vision, and decreased night vision while taking Accutane.

If you have any of these events or any other unusual or serious problems while on Accutane, discontinue taking Accutane and check with your prescriber immediately. While these changes do not happen often, they may be signs or symptoms of other serious conditions and if left untreated, could

possibly result in permanent effects. While waiting to talk to your prescriber you can stop taking Accutane.

ESPECIALLY FOR FEMALE PATIENTS

READ THIS AND THE OTHER MATERIAL GIVEN TO YOU BY THE PRESCRIBER

AVOID PREGNANCY WARNING TO ALL FEMALE PATIENTS

YOU MUST NOT TAKE ACCUTANE IF YOU ARE PREGNANT, PLAN TO BECOME PREGNANT, OR UNEXPECTEDLY BECOME PREGNANT DURING ACCUTANE TREATMENT. Severe birth defects are known to occur in babies of females taking Accutane in any amount even for short periods during pregnancy. There is an **extremely high risk that a deformed baby** will result if you become pregnant while taking Accutane; many babies have died. Potentially any exposed baby may be affected. There is also an increased risk of miscarriage. Premature births have occurred.

You and your prescriber must rule out the possibility that you may be pregnant before you start Accutane therapy. You must have urine or blood pregnancy tests done while you are in your prescriber's office that shows you are not pregnant. Before you receive your Accutane prescription, you must have another urine or blood test to confirm that you are not pregnant. This test must be either on the second day of your next period (menses) or 11 days after your last unprotected sexual intercourse during which you did not use birth control; whichever is the later calendar date. Only then can your prescriber give you a prescription so you can begin your Accutane therapy.

Effective birth control is necessary during Accutane treatment. You must discuss effective birth control with your prescriber or ask about a free referral to a birth control specialist. **Two separate, effective forms of birth control are to be used at the same time** for at least 1 month before beginning therapy and during therapy, and must be continued for 1 month after Accutane treatment has stopped. Any birth control method can fail. Although oral contraceptives (birth control pills) and injectable/implantable birth control products are the most effective; all forms of birth control have occasionally failed. Therefore, it is critically important that you use two separate and effective forms of birth control at the same, even when one is the birth control pill. Even if you think you cannot become pregnant, you must use birth control.

There are only two exceptions to using two forms of separate, effective birth control; the first is if you have had a hysterectomy. The second is if you are able to commit to full and complete abstinence. Abstinence means that you are sure that you will have no sexual contact whatsoever before, during, and for one month after Accutane treatment.

What are other possible or reasonably likely side effects of Accutane?

All Patients should be aware that most patients have dry skin, chapped lips, dry eyes, and dry nose while taking Accutane. You may have some discomfort with these conditions. Some patients have changes in their blood sugar or the amount of fat (lipids) in their blood. Your prescriber will check you for all these symptoms.

What is Accutane?

Accutane is a medication that should only be taken by patients who have the most severe form of nodular acne that cannot be treated with other medications. Severe nodular acne is a form of acne that has several to many nodules, which are small acne lumps about the size of a pencil eraser. Accutane is to be taken only when all other forms of treatment have been unsuccessful, including antibiotics that you take by mouth. Before you decide to take Accutane, you must have discussed with your prescriber the types of deformed babies that can occur if you are pregnant or may become pregnant while taking Accutane.

How should I take Accutane?

- Be sure to take your medication as directed by your prescriber. Read the prescription label on the package carefully. If there is anything you do not understand, ask your prescriber or pharmacist to explain it to you.
- Accutane has been prescribed specifically for you – **DO NOT SHARE ACCUTANE WITH OTHER PEOPLE.** In addition, **DO NOT GIVE BLOOD** while you are taking Accutane or for one month after stopping Accutane treatment. If someone else, who is pregnant, receives your donated blood, her baby may be exposed to Accutane and may suffer severe birth defects.
- Do not breast feed while taking Accutane and for one month after stopping Accutane treatment
- Take Accutane twice a day with food or as directed by your prescriber.
- Some patients may have temporary worsening of their acne but should continue to take Accutane unless instructed otherwise by their prescriber.

Who should not take Accutane?

The most serious effect of Accutane is that it causes birth defects. **You must not take Accutane if you are pregnant, plan to become pregnant, or unexpectedly become pregnant during Accutane treatment. All women should read the section ESPECIALLY FOR FEMALE PATIENTS in this Medication Guide for additional information and warning about Accutane and pregnancy**

Do not take Accutane unless you have severe nodular acne that cannot be treated with other medications.

What should I avoid while taking Accutane?

AVOID PREGNANCY – Use two separate, effective forms of birth control

General advice about prescription medications:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns about Accutane, ask your prescriber. Your prescriber or pharmacist can give you information about Accutane that was written for health care professionals. Do not use Accutane for a condition for which it was not prescribed. Do not share Accutane with other people. This Medication Guide is only a summary of important information. This medication guide does not include all warnings, precautions, adverse reactions or side effects that you may experience. Always speak with your prescriber about your medication. This information does not take the place of talking with your prescriber.

Active Ingredient: Isotretinoin. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide

THIS MEDICATION GUIDE HAS BEEN APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION

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Investigations Evaluating Psychiatric Adverse Events in Accutane-Treated Patients

1. Pharmacoepidemiological Safety Assessment of Spontaneous Reports

Objective: The Accutane (Isotretinoin) -Psychiatric Disorder Issue Work-Up conducted by Robert Nelson, PhD, included an epidemiological review and analysis of all of the spontaneous reports received by Roche between 1982 and April 30, 1999. The objective of this study was to determine the nature and extent of any relationship between Accutane therapy and psychiatric morbidity.

Methods: The objectives were addressed by describing the types of reported psychiatric disorders, identifying all associated risk factors contained in the reports, assessing the magnitude of the identified risk factors, and evaluating causality within the pharmacoepidemiologic framework. The review of spontaneous reports involved an evaluation of the reports for category, quality, and content, and to determine the value of the reports in explaining proposed relationships. The epidemiological analyses involved evaluation of the relative likelihood of all risk factors identified and formulation of conclusions based on epidemiological methods (observed versus expected rates, etc.).

Results:

Mood Disorder: Of 1,247 mood disorder reports: there were 367 dechallenge reports (23 positive dechallenge and rechallenge, and 37 reports with mood disorder diagnosis subsequent to exposure). Even the dechallenge reports had a high level of diversity/inconsistency. At the individual case level, a small number of cases imply a causal association between depressive symptoms and/or mood disorders, and Accutane. However an assessment in the context of the natural history and alternative risk factors provides strong supporting evidence that the described symptomology and disorders are much more likely to be due to factors other than Accutane

Psychotic Disorder: Of 120 psychotic disorder reports, there were 20 dechallenges, 5 positive dechallenge and rechallenges; the 100 remaining reports included 9 additional reports with diagnosis. There was no pattern of consistency in the available data. At the individual case level, at least 3 reports imply a causal association between the described psychotic disorder and Accutane. Other factors provide alternative explanations in the majority of reports.

Suicidal Behavior: There was a total of 168 reports of suicidal behavior (1982 to April 30, 1999), with 104 reported suicide attempts and 64 reported suicides. Overall, the suicide reports were poorly documented; none had psychological autopsy. There was no apparent dose relationship. The ratio of male to female was 5 to 1 for reports of completed suicide. None of the 168 reports imply causality between suicidal behavior and Accutane, at the individual case level.

Epidemiological Analyses: Epidemiological analyses resulted in the following prevalence estimates for psychotic disorders in Accutane-exposed: 1% (25,000) in ages 15-24, 2% (14,000) in ages 25-34; in addition, alcohol and drug abuse prevalence rates (16-20%) result in an increased risk factor for developing psychiatric conditions in the exposed Accutane cohort. Comparison of observed suicide frequency versus that expected demonstrated that the observed number of suicides is less than expected. For example, in males there were 27 suicides observed in the under age 25 group, while 262 could be calculated based on the prevalence data for this population.

Conclusions: The analysis of spontaneous reports demonstrated: no consistent patterns in the data, complex environment of background symptoms, very high background rates of disease,

very high background rates of alternative risk factors. Therefore, there is no evidence in these data to support a causal relationship between Accutane and psychiatric disorders.

2. Analyses of Beck Depression Inventory (BDI-II) Assessment Results in Clinical Trial, Protocol NR15645

Objective: The clinical trial NR15645 was a double-blind, randomized, parallel-group, multicenter study conducted to compare the clinical efficacy of Accutane NF and Accutane®. Although primarily an efficacy study, a full safety evaluation was done which included, in addition to recording spontaneous adverse events, the use of a validated instrument, the Beck Depression Inventory (BDI-II), to monitor the possible occurrence of depression during the course of the trial.
Methods: The BDI-II was administered at baseline and upon completion of the treatment period or at intermediate time points if warranted by the response to a 4-item Mood/Depression Assessment Questionnaire. These data were reviewed relative to Accutane use.
Results: The two treatment groups were essentially identical in depression scores: Accutane NF-treated patients' mean scores decreased from 3.5 ± 4.6 at baseline to 1.7 ± 3.1 at Week 20, compared to 3.6 ± 4.5 and 1.9 ± 3.7, respectively, for Accutane®-treated patients at baseline and Week20. The great majority of scores were consistent with the category of "minimal" depression. No patient scored 31 or greater, which represents "severe" depression and would require withdrawal from the study.
Conclusion: Results in this trial do not indicate an association between Accutane use and depression.

3. Jick SS, et al. Isotretinoin Use and Risk of Depression, Psychotic Symptoms, Suicide, and Attempted Suicide. Arch. Dermatol. Vol 136:1231-1236, 2000.

Objective: To further investigate the possibility of an association between isotretinoin therapy and the risk of depression, psychotic symptoms, suicide, and attempted suicide using a nested cohort epidemiological study design.
Methods: A large population-based cohort study was designed using the Canadian Saskatchewan Health Database and the United Kingdom General Practice Research Database. Data were analyzed for 7,195 isotretinoin users and 13,700 oral antibiotic users with acne from Canadian Saskatchewan Health Database and from 340 isotretinoin users and 676 oral antibiotic users with acne from the United Kingdom General Practice Research Database. Data were reviewed from between 6 months and 5 years before, and at least 12 months after, their first isotretinoin or antibiotic prescription. Prevalence rates of neurotic and psychotic disorders, suicide, and attempted suicide were compared between isotretinoin and antibiotic users and within isotretinoin users as their own comparison (pretreatment vs. posttreatment).
Results: Relative risk estimates, comparing isotretinion use and oral antibiotic use with nonexposure to either drug for newly diagnosed depression or psychosis, were approximately 1.0 regardless of the data source. Similarly, relative risk estimates were all around 1.0 when comparing before with after isotretinoin use. The relative risk estimate for suicide and attempted suicide was 0.9 (95% confidence interval, 0.3-2.4) when comparing current isotretinoin exposure with nonexposure. There were no completed suicides in the Accutane exposed group.
Conclusion: This study provides no supportive evidence that use of isotretinoin is associated with an increased risk for psychiatric disorders.

4. Review of Psychiatric Adverse Events in Accutane Users and Matched Non-Users, UnitedHealthcare Plan Members

Objectives: A retrospective claims database study was conducted using data from the UnitedHealthcare Research Database, including Florida, Ohio, and Rhode Island plan units, April 1995 through September 1999. In this study, all possible Accutane-associated adverse events, including psychiatric adverse events, were tracked and incidence rates were determined.
Methods: The study included 5,130 Accutane users and 25,600 non-users matched on age, gender, and plan unit. Eight definitions for flagging depression from a claims database, using office visit claims and/or psychiatric drug dispensing claims, were tested and evaluated in the database. Patients were tracked from April 1, 1995 through September 30, 1999, with 6 month screening period observed prior to April 1, 1995 for the purpose of identifying pre-existing disease. Accutane patients were followed to 30 days after last Accutane drug supply or to study end date of September 30, 1999, whichever came first. Non-users were followed for corresponding time periods. Overall, health care use rates, measured by number of physician office visits, was determined to be a confounding factor in depression rates, and was controlled for in the analyses
Results: At screening, a higher rate of underlying psychiatric illness overall was observed in Accutane users than in non-users, 13.5% versus 9.5% ($p < .0001$); and specifically, a higher rate of depression defined as depression diagnosis or antidepressant dispensing was also observed in this time period, 9.1% versus 5.7%. However, it is recognized that a 6 month screening period is too short to accurately estimate depression history, therefore these rates represent an underestimate. As seen in other claims database analyses of this type, number of office visits was found to be a confounding factor in the analyses (i.e., patients obtaining more medical care in general, will also be more likely to obtain medical care for psychiatric illness). Stratified by the confounding factor of office visit use, no higher incidence rates (outside of confidence intervals for incidence rates in Accutane users) were observed in Accutane users versus non-users, for each of the 8 depression definitions. For some of the depression definitions, there were times when the incidence rate for non-users were higher than that for Accutane users (and outside of associated confidence intervals). There were no completed suicides. There were 10 attempted suicides, all of which appear to have a preexisting psychiatric condition and/or substance abuse either concurrently and/or by history.
Conclusion: Even with minimal control for psychiatric history, there does not appear to be sufficient evidence that there is any increase of depression in the Accutane treated group as compared to matched non-user group, when controlling for confounding of medical care utilization.

5. Prescription Sequence Symmetry Analyses of Accutane versus Antidepressant Dispensings

Objectives: A prescription sequence symmetry analysis of Accutane versus antidepressant dispensings was performed using pharmacy claims data from Synergy, from June 1, 1999 through March 31, 2000.
Methods: The analysis evaluated the prescription order of Accutane and antidepressants. A symmetrical distribution of Accutane and antidepressants prescribed first would indicate a non-causal relationship between Accutane use and depression. A nonsymmetrical distribution of prescription order (i.e., Accutane prescribed first more than antidepressants) would be indicative of a possible depression-inducing effect. Changes in the general prescribing patterns of antidepressants throughout the study timeframe were taken into account in the adjusted rate

ratios. For comparative purposes, a similar analysis was done for minocycline versus antidepressant use.

Results: The data comprised all prescriptions recorded by the 17,348 patients using both Accutane and antidepressants in the time period, June 1, 1999 through March 31, 2000, and all prescriptions recorded by the 7,360 patients using both minocycline and antidepressants in this time period. Results of this analysis revealed no significant asymmetry in the prescription order of Accutane and selective serotonin reuptake inhibitors (SSRIs) (rate ratio = 0.99; 95% CI = (0.93, 1.06)), Accutane and amine antidepressants (rate ratio = 0.90; 95% CI = (0.78, 1.04)), or Accutane and "other" antidepressants (rate ratio = 0.95; 95% CI = (0.85, 1.05)). When all antidepressant classes were combined, the prescription orders were symmetrical (rate ratio=0.97, 95% CI=(0.92, 1.02).

Similar results were obtained for the minocycline analyses. Results indicated no significant asymmetry in the prescription order of mnocycline and amine antidepressants

Conclusions: The results of these analyses indicate a non-causal relationship between Accuatane use and depression, and between minocycline use and depression.

6. Clinical Psychiatric Analyses of Spontaneous Report Cases

Objectives: Douglas Jacobs, MD, Associate Clinical Professor of Psychiatry, Harvard Medical School, performed a clinical analysis of spontaneous reports from the Accutane Medwatch Reports

Methods: The analysis involved a psychological autopsy to identify risk factors: subsyndromal psychopathology, past suicidality, familial psychiatric disorder, legal/disciplinary problems, presence of firearm (or other lethal method). The objective of the study was to address the following research questions: (1) Is there any pattern to suicide reports in relationship to Accutane?, for example, gender distribution and on versus off Accutane, (2) What is the significance of the temporal association with "depression"?, (3) Does Accutane exacerbate underlying psychopathology and lead to suicide?, (4) Does Accutane cause impulsive suicides? Suicides in Medwatch Reports were classified according to the following categories: (1) relationship to Accutane use, (2) concealment of symtoms, (3) confounding factors, e.g., pre-existing psychiatric history, (3) no apparent psychopathology, (4) miscellaneous.

Results:

Suicide On/Off Accutane: 30 cases were on Accutane, including 4 that were on Accutane over 6 months. 24 cases were off Accutane and 10 were unknown. No evidence of predominance of on/off factor. Gender was total males of 53, total females of 11. Total suicides were consistent with known demographics. On/off ratio was the same, regardless of gender.

Depression occurring while on Accutane: 17 of the 64 reports. 10 cases committed suicide on Accutane. 7 cases committed suicide off Accutane. Only one case had psychiatric treatment.

Prior Psychiatric History Related to On/Off Accutane: 9 cases on Accutane and 12 cases off Accutane had prior psychiatric history. In review of reports with prior psychiatric history that represent "controls", the following was observed: none of these reports developed symptoms of underlying illness while on Accutane, Accutane did not precipitate symptoms in persons at-risk, suicide unrelated to Accutane, and conclusion was that suicide was related to underlying psychiatric disorder.

Conclusions: Review of Medwatch database indicated: (1) no alteration of gender distribution, (2) no impact of on/off Accutane, (3) no significant relationship to concurrent "depression", (4) no exacerbation of underlying psychiatric disorders, (5) lack of warning signs consistent with youth suicide, (6) no evidence of impulsive factor.

Overall Summary:

The combination of independent different methods of analysis are all similar in that they provide a body of evidence suggesting no association of developing these psychiatric conditions and the use of Accutane. Overall, data from over 33,000 Accutane users were evaluated in the above investigations to draw the conclusion that in the context of the natural history and alternative risk factors the described psychiatric conditions can be more likely attributed to factors other than Accutane.

Psychiatric Study Design Committee (proposed)

Contact	Affiliation	Specialty
Dr. R.M. Kessler	Harvard Medical School; Dept Health Care Policy	Epidemiologist/psychiatric epidemiology trials
Dr. S. Montgomery	Imperial College of Medicine, St Mary's Hospital, London, UK	Psychiatrist; Brief recurring depression
Dr. D Bickers	Columbia University School of Medicine Dept of Dermatology	Dermatologist Editor: Investigative Dermatology
Dr. D. Jacobs	Harvard Medical School Dept of Psychiatry	Suicidologist
Dr. J. Koo*	Stanford University Medical School Dermatologist	Board certified Dermatologist/Psychiatrist
Dr. R. Neal*	University of Pittsburgh Medical Center Dept of Psychiatry	Adolescent psychology Atypical depression
J. Endicott*	Columbia University Dept of Psychiatry	Major depressive disorders
K Merikangas*	Yale University Dept of Psychiatry and Epidemiology	Epidemiology of psychiatry
D J Nutt	University of Bristol School of Medical Sciences Bristol, England	Professor of Psychopharmacology Dean of Clinical Medicine

*** Note these individuals have not yet been contacted for this activity**